s8a.m5.o1 **The Molecular Mechanism of Muscle Contraction**. K.C. Holmes, *Max Planck Institute for Medical Research, 69120 Heidelberg, Germany*.
Keywords: actin, myosin, conformers.

The contraction of voluntary muscles takes place by the mutual sliding of two sets of interdigitating myosin (thick) filaments and actin (thin) filaments organized in sarcomeres. The relative sliding is brought about by "*cross bridges*" , elements of the myosin molecules which protrude from the myosin filaments and interact cyclically with the actin filaments, transporting them by a rowing-like action. During the process ATP (adenosine triphosphate) is hydrolyzed to ADP (adenosine diphosphate).

However, myosin is a product-inhibited ATPase. The release of phosphate and ADP is stimulated by binding to actin. This mechanism was first elucidated by Lymn and Taylor[1]. who combined their results with the swinging cross-bridge proposals of HE Huxley[2] to propose a cyclic model of cross-bridge activity:

1. In the absence of nucleotide the myosin cross bridge binds tightly to the actin filament to form the "strong" or "rigor" complex.
2. The binding of ATP to the ATPase site on the myosin cross-bridge rapidly dissociates the actomyosin complex; myosin then hydrolyzes ATP to form a stable myosin-products complex ($ADP.P_i$).
3. Actin recombines weakly with this complex and then isomerises to strong binding.
4. Strong actin binding releases the products and is accompanied by the cross bridge "swing" which "rows" the actin filament past the myosin filament.

Crystallographic studies reveal two conformers of the cross bridge, OPEN and CLOSED (see [3] for references). OPEN and CLOSED refer to small changes (0.5nm) in the active site associated with the presence or absense of the γ-phosphate. A striking difference between OPEN and CLOSED is in the orientation of the long C-terminal "neck" which acts as a lever arm to magnify the small changes in the active site to a 10nm movement at the distal end of the lever.

Cross bridges bind strongly to actin produce "decorated actin", which is a convenient model for the strong actin-myosin interaction. Electron microscopy reveals that the neck can act as a "lever arm". The switching between the conformations OPEN and CLOSED appears to be the basis of muscle contraction. During the cyclic interaction with actin, the cross-bridge binds first weakly to actin and then strongly. Crystallographic studies do not reveal the structural basis of the weak to strong transistion. However, cryo-electronmicroscopic images of decorated actin at high resolution obtained using energy filter microscopy (Schroeder, Holmes et al *in preparation*) show the nature of this transition.

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s8a.m5.o2 **Rotary mechanism of ATP synthase.** J.E. Walker, *Medical Research Council, Dunn Human Nutrition Unit, Hills Road, Cambridge, CB2 2XY, UK.*
Keywords: macromolecular assemblies.

The ATP synthase from mitochondria, bacteria and chloroplasts is a complex multi-subunit enzyme that works by a rotary mechanism. The lecture will describe how structural changes in the catalytic F_1- domain are impelled by the rotation of a central α-helical structure in γ-subunit. The γ- subunits forms part of a central stalk linking F_1 to the F_o membrane domain and the δ- and and ε-subunits are also associated with it. The exposed region of the central stalk resembles a riding boot, with the foot in contact with a ring of 10 c-subunits in the F_o membrane domain [2]. The details of the central stalk have been resolved to high resolution in DCCD inhibited MF_1 [3]. The interface between the foot and the c-ring is extensive, suggesting that the γ-, δ-, ε- subunits and the c-ring rotate as an ensemble. Proposed mechanisms of rotation require the participation of both subunit c and subunit a, another membrane component. As the structure of subunit a remains unknown, the precise mechanism of coupling of the transmembrane proton motive force to rotation remains a mystery.

The lecture will also discuss how covalent and non-covalent inhibitors act by interfering with rotation. The mode of action of IF_1, the natural protein inhibitor, remains unknown. However, it is clear that it has two oligomeric states, an inactive tetramer at high pH and an active dimer at below pH 6.5 [4].

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